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COMPLETE SPECIFICATION

Stannous Phosphonates and their use in Oral Compositions for Caries Prophylaxis

We, THE PROCTER & GAMBLE COMPANY, a corporation organised under the laws of the State of Ohio, United States of America, of 301 East Sixth Street, Cincinnati, Ohio, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel stannous salts of gem-diphosphonic acids and to stable oral compositions for caries prophylaxis which contain such salts in conjunction with a water-soluble source of fluoride ions.

By the term "oral composition" as used herein is meant a product which in the ordinary course of usage is not intentionally ingested, but is retained in the oral cavity for a time sufficient to contact substantially all of the dental surfaces. Such products include, for example, dentifrices, mouthwashes, chewing gums, and dental prophylaxis pastes and topical solutions for application by a dentist.

It is known that certain metallic ions have a significant effect on the anticariogenic efficacy of oral compositions. For example, a body of scientific literature shows that the use of a source of stannous ions in conjunction with fluoride gives a more effective anticariogenic product than is attained with fluoride alone [J. C. Muhler et al., J.A.D.A. 51, 665 (1955)].

One of the problems which has developed in the formulation of stable oral compositions containing tannous tin, especially aqueous compositions, is the propensity of this metal to oxidize to its higher valence state, hydrolyze to stannous hydroxide and/or react with other constituents of the composition to form very stable complexes or highly insoluble compounds. The occurrence of any of the foregoing can render tin non-reactive with

dental enamel. Stannous tin in this non-reactive state is referred to herein as "unavailable."

Various approaches have been used to maintain stannous tin in dental enamel reactive form. For example, U.K. patent specification No. 804,486 discloses the use of a sparingly soluble stannous salt such as stannous pyrophosphate as a "reservoir" of stannous ion in conjunction with the water-soluble stannous salt such as stannous fluoride. As stannous ion derived from the soluble salt reacts with dental enamel or becomes unavailable through e.g. hydrolysis, the sparingly soluble stannous salt slowly dissolves to replace the depleted stannous ion. However, the pyrophosphate anion hydrolyzes to orthophosphate on aging with the result that the "reservoir" capacity of stannous pyrophosphate gradually diminishes.

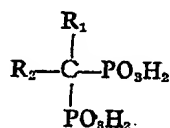
U.K. patent specification No. 1,009,480 discloses an advance over specification No. 804,486 involving the maintenance of dental enamel-reactive stannous tin by complexing Sn(II) ion with an aldonic acid to form a water-soluble stannous aldinate. A similar approach to the preservation of stannous tin in a stable and available form is the use of stannous complexes of hydroxyethylnitridiacetic acid, *meta*-hydroxy benzoic acid, 1,2,3-propanetricarboxylic acid, itaconic acid, or malic acid for this purpose. These complexes are characterized by their solubility in aqueous solution and the strength of these complexes is such that stannous tin is protected from inactivating influences, yet is not so strong as to prevent reaction with dental enamel. Thus, this approach to maintenance of stannous tin represents a compromise between stability and reactivity, with the result that the stannous tin derived therefrom is not as available for reaction of dental enamel as would be the case with a less stable complex.

It has now been found that yet another and

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more effective approach to the maintenance of reactive stannous tin exists which involves the provision of certain sparingly soluble organic stannous salts which slowly dissolve to yield weak stannous complexes. These complexes are more reactive with dental enamel than the prior art soluble complexes yet the anions are more stable to hydrolysis than the pyrophosphate of specification No. 804,486 which results in greater stability on aging. Thus, the advantages of both prior art approaches to maintenance of stannous tin can be realized in the approach herein provided.

According to the present invention, there are provided distannous salts of gem-diphosphonic acids having the formula



wherein R_1 is hydrogen, halogen, hydroxyl, benzyl, alkyl, hydroxyalkyl, methoxyalkyl or carboxyalkyl and has up to 12 carbon atoms and R_2 is hydrogen, halogen, hydroxyl, acetyl, phenyl, benzyl, alkyl, hydroxyalkyl, methoxyalkyl or carboxyalkyl and has up to 12 carbon atoms.

Also according to the present invention there is provided an oral composition for caries prophylaxis comprising

- (a) at least one water soluble fluoride in a quantity sufficient to provide from 25 to 4000 and preferably from 100 to 4000 parts of fluoride ion per million parts by weight of the composition, and
- (b) from 0.05% to 5.0% by weight of at least one distannous salt of a gem-diphosphonic acid as just defined.

In this specification all parts and percentages are by weight unless otherwise specified.

In addition to the advantages which the stannous salts of this invention provide from the standpoint of maintaining stannous tin in a stable and reactive form, they also serve to retard the development of dental calculus by interfering with calcium hydroxyapatite crystal growth. Oral compositions containing such salts therefore provide both improved anticaries and anticalculus effects.

The gem-diphosphonic acids from which the stannous salts of this invention are derived can be prepared for example by alkylation at the central carbon atoms of tetra-alkyl methane diphosphonates with an alkyl halide in accordance with the method described by G. M. Kosolopoff in *J. Amer. Chem. Soc.*, 75, 1500 (1953). Preferred methods of preparing alternative gem-diphosphonic acids are disclosed in U.K. patent specification No. 1,026,366 and in copending application No. 34,223/66 (Serial No. 1,138,238).

The distannous salts of the gem-

diphosphonic acid may be prepared by mixing an aqueous solution of a gem-diphosphonic acid with at least a stoichiometric amount of an aqueous solution of a stannous salt, preferably stannous chloride, precautions being taken to exclude atmospheric oxygen, recovering and washing and drying the precipitate.

Several representative stannous salts of gem-diphosphonic acids prepared in accordance with this invention are set forth in the following Examples.

EXAMPLE I

The distannous salt of methanediphosphonic acid was prepared in the following manner: 35.2 g. of 99.8% pure methanediphosphonic acid were dissolved in 1,000 ml. of oxygen-free distilled water under a nitrogen blanket. 81.0 g. of 93.6% pure $SnCl_2$ (anhydrous) were then dissolved in 750 ml. of oxygen-free distilled water under a nitrogen blanket. The $SnCl_2$ solution was then added to the methanediphosphonic acid solution with vigorous agitation. After three minutes of agitation the precipitate was recovered by filtration through a Buchner funnel under a nitrogen blanket. The precipitate was washed three times with anhydrous acetone, after which the acetone was removed by evaporation. The yield was 76 g. which analyzed as follows:

	Found	Theoretical	
Carbon	3.2	2.93	90
Hydrogen	1.0	0.49	
Phosphorus	14.3	15.15	
Stannous tin	53.6	58.0	

EXAMPLE II

The distannous salt of ethane-1-hydroxy-1,1-diphosphonic acid was prepared as follows: 51.6 g. of ethane-1-hydroxy-1,1-diphosphonic acid (prepared in accordance with the process disclosed in U.K. patent application No. 34,223/66 (Serial No. 1,138,238) were dissolved in 750 ml. of oxygen-free distilled water, under a nitrogen blanket. 99.4 g. of $SnCl_2$ (anhydrous, 99% pure) moistened with 20 ml. of 12N HCl were dissolved in 500 ml. of oxygen-free distilled water under a nitrogen blanket.

The $SnCl_2$ solution was added to the ethane-1-hydroxy-1,1-diphosphonic acid solution rapidly and with vigorous agitation. After three minutes of agitation following the addition, the precipitated salt was filtered off using a suction filter, under a nitrogen blanket. The solid was washed three times, with dry acetone. Product yield was 57.9 g. which analyzed as follows:

	Found	Theoretical	
Carbon	5.3	5.46	120
Hydrogen	1.2	0.91	
Phosphorus	12.9	14.1	
Total Sn	51.4	54.0	

- stirring propeller is about 1/2" above the teeth in the beaker, maintaining the propeller at this height throughout the test. A 40 ml. aliquot of lactate buffer is added to the mounted tooth set and the stirrer is started. After 15 minutes, the lactate buffer is removed, saved for analysis, and the tooth mounts are rinsed three times in distilled water and replaced in the water bath for the treatment step.
- A 15 gram portion of the test dentifrice is mixed with about 45 ml. of water and this mixture is centrifuged for 15 minutes. A 40 ml. aliquot of the supernatant from the centrifuged dentifrice slurry is added to the tooth set and the stirrer is started. At the end of five minutes of treatment, the stirring is stopped and the treatment solution is discarded. The teeth are rinsed in distilled water and exposed to another 40 ml. of lactate buffer stirred at 1725 R.P.M. for 15 minutes.
- This post-treatment lactate solution and the pre-treatment lactate solution are analyzed for phosphorus using the method of Martin and Doty. The percentage of enamel solubility reduction is computed as the difference between the amount of phosphorus in the pre-treatment and post-treatment lactate buffer solutions divided by the amount of phosphorus in the pre-treatment lactate buffer solution.
- Formulations of various toothpaste Examples of this invention are set forth in Table I below and the aging and ESR data obtained thereon are presented in Table 2. The numbers set forth in Table 1 refer to concentration in percent by weight. The numeric values (other than ESR and pH values) refer to p.p.m. of soluble stannous tin. The designation "As is" in Table 2 refers to the pH specified in parenthesis.

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When aged at 50°C the control composition set forth in Table 1 yields the following values:

Fresh	2 days	3 days	4 days	7 days	% ESR	
483 (4.7)	232	96	100	45	Fresh	66.8
867	297	132	81	35	30 days	35.0

It can be seen that the Sn(II) level of the control composition was reduced over 50% after only two days of aging. After seven days of aging at 50°C., the Sn(II) level of the control was reduced to less than one-tenth of its original level. A corresponding reduction in ESR value is seen in the aged control toothpaste.

The toothpastes of the foregoing Examples on the other hand provide a relatively constant level of Sn(II) after aging even under these severe storage conditions for even longer periods (28 days). The ESR values shown

above for several of the examples are seen to be substantial even after this period of aging.

The toothpastes of Examples IV and V provide significant reductions in dental calculus formation as compared to the control composition when used in the conventional manner.

Other oral compositions in accordance with this invention are formulated as follows:

EXAMPLE XXI

A mouthwash composition is prepared by mixing the following components using conventional means.

Component	% By Weight
Ethyl alcohol (50% ethanol, 50% water)	83.00
Glycerine	12.00
Methyl triethanol ammonium fluoride	2.88
Distannous ethane-1-hydroxy-1,1-diphosphonate	1.15
Flavouring	0.85
Saccharin	0.12
pH adjusted to 6.5	

Prior to use this composition is diluted by adding 2 ml. of the concentrate to 20 ml. of water. This composition contains high levels of dental enamel reactive Sn(II) over substantial periods of time and yields a substantial reduction in enamel solubility, even after aging. Thus, this composition provides an effective means for caries prophylaxis when used in the usual manner two or more times a day.

The distannous ethane-1-hydroxy-1,1-diphosphonate of this Example can be replaced by distannous propane-2,2-diphosphonate, distannous methanethoxydiphosphonate, distannous dichloromethylenediphosphonate, distannous bromomethylenediphosphonate, or distannous methanephnylhydroxydiphosphonate in quantities sufficient to provide equivalent Sn(II) levels with good results.

EXAMPLE XXII

Another mouthwash embodiment of the invention is formulated as follows:

Component	% By Weight
Ethanol	35.00
Glycerine	10.00
Laurylamine hydrofluoride	0.72
Stannous chloride	0.016
Distannous methane diphosphonate	0.15
Flavouring	0.16
Saccharin	0.12
Water	Balance
pH adjusted to 6.0.	

5 This mouthwash contains effective concentrations of enamel-reactive stannous tin over a period of several months. When used in the conventional manner in undiluted form this composition substantially reduces enamel solubility and caries incidence.

Distannous nonane-5,5-diphosphonate, distannous decane-1,1-diphosphonate, distannous dodecane-2,2-diphosphonate, distannous tetradecane-3,3-diphosphonate, or distannous butane-1,1-diphosphonate can be used in place of distannous methane diphosphonate with comparable results.

EXAMPLE XXIII

A chewing gum is prepared having the following composition.

Component	% By Weight
Gum base*	21.50
Sugar	59.50
Corn Syrup (Baume 45)	18.20
Flavouring	q.s.
Sodium fluoride	0.25
Distannous pentadecane-8,8-diphosphonate pH adjusted to 4.5	0.55

*Ester gum	30 parts
Coumarone resin	45 parts
Latex (dry)	15 parts
Paraffin wax (M.P. 180°F.)	10 parts

TABLE

Ex.	Liquids			Abrasives			Sn ₂ EHDP	Sn ₂ MDP
	H ₂ O	Sorbo ¹	Glycerine	Ca ₂ P ₂ O ₇	MUF ²	UF ³		
IV	25.7	19.6	9.8		14.7	22.5		0.98
V	26.19	19.6	9.8		14.7	22.5		0.49
VI	26.44	19.6	9.8		14.7	22.5		0.245
VII	23.4	21.6	10.8		14.9	22.3		0.49
VIII	22.83	21.6	10.8		14.9	22.3		0.25
IX	25.5	19.38	9.69	37.8				0.48
X	26.37	19.38	9.69	37.8				0.24
XI	26.13	19.38	9.69	37.8			0.48	
XII	25.04	20.0	10.0		15.0	23.0		0.1
XIII	25.01	20.0	10.0		15.0	23.0		0.25
XIV	21.88	22.0	11.0		15.2	22.8		0.1
XV	25.43	20.0	10.0		15.0	23.0		0.1
XVI	26.30	19.4	9.7	37.83			0.24	
XVII	20.06	19.4	9.7	37.83			0.48	
XVIII	26.17	19.4	9.7	37.83				0.375
XIX	26.17	19.4	9.7	37.83			0.375	
XX	26.37	19.4	9.7	37.83				0.17
Control ⁹	25.60	19.4	9.7	37.8				

1. Sorbitol—30% aqueous solution
2. Precipitated melamine-urea-formaldehyde condensation product
3. Precipitated urea-formaldehyde condensation product
4. Sodium lauryl sulphonate
5. Sodium coconut monoglyceride sulphonate
6. Sodium carboxymethylcellulose
7. Magnesium aluminium silicate
8. Hydroxyethylcellulose
9. Control is a commercially available stannous fluoride containing dentrifice which contained 0.97% by weight of stannous pyrophosphate in addition to the recited components.

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TABLE 2
Time Interval at 50°C.

Example	Fresh	2 days	7 days	14 days	21 days	28 days	% ESR
IV	As is: 922 (4.4) pH 6.2 1655	802 (4.1) 1720	820 (4.1) 1617	—	767 (4.2) 1744	582 (4.4) 1770	28 days 70.5
V	As is: 910 (4.2) pH 6.2 957	737 1084	717 (4.3) 982	—	752 (4.3) 1096	671 (4.3) 1031	28 days 64.6
VI	As is: 826 (4.3) pH 6.2 537	723 (4.5) 532	582 (4.6) 540	652 (4.5) 642	—	641 (4.2) 666	—
VII	As is: 956 (3.6) pH 6.2 853	—	577 807	528 685	—	457 (3.8) 688	—
VIII	As is: 911 (3.7) pH 6.2 393	—	469 (3.7) 373	523 (3.7) 443	—	435 (3.8) 398	—
IX	As is: 793 (4.2) pH 6.2 926	—	448 (4.9) 567	478 (5.0) 575	—	474 (5.1) 523	—
X	As is: 529 (4.3) pH 6.2 564	280 (4.6) 365	257 (5.1) 281	257 (5.1) 265	—	210 (5.2) 225	Fresh 30 days 69.0 52.3
XI	As is: 631 (4.3) pH 6.2 730	—	442 (4.6) 424	422 (4.8) 434	—	406 (4.7) 400	—
XII	As is: 688 (4.4) pH 6.2 313	628 (4.3) 395	540 (4.4) 470	502 (4.3) 443	—	466 (4.3) 417	Fresh 30 days 65.5 73.9
XIII	As is: 212 (4.8) pH 6.2 225	212 (4.8) 205	—	183 (4.8) 173	148 158	153 (4.8) 162	Fresh 30 days 47.8 54.9
XIV	As is: 702 (4.5) pH 6.2 188	711 (4.3) 185	593 (4.2) 197	526 (4.3) 276	448 (4.1) 281	—	Fresh 30 days 69.8 74.1
XV	As is: 83 (4.9) pH 6.2 92	59 (4.9) 47	44 (4.9) 40	32 (4.8) 43	35 (4.8) 43	—	Fresh 30 days 30.4 40.2
XVI	As is: 513 (4.8) pH 6.2 490	363 (4.8) 375	295 (5.2) 291	274 (5.3) 284	248 (5.6) 227	—	Fresh 30 days 60.6 41.4
XVII	As is: 755 (4.6) pH 6.2 807	—	519 (4.9) 540	487 (5.1) 532	—	466 (5.3) 505	Fresh 30 days 64.8 40.2

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above for several of the examples are seen to be substantial even after this period of aging.

The toothpastes of Examples IV and V provide significant reductions in dental calculus formation as compared to the control composition when used in the conventional manner.

Other oral compositions in accordance with this invention are formulated as follows:

EXAMPLE XXI

A mouthwash composition is prepared by mixing the following components using conventional means.

Component	% By Weight
Ethyl alcohol (50% ethanol, 50% water)	83.00
Glycerine	12.00
Methyl triethanol ammonium fluoride	2.88
Distannous ethane-1-hydroxy-1,1-diphosphonate	1.15
Flavouring	0.85
Saccharin	0.12
pH adjusted to 6.5	

Prior to use this composition is diluted by adding 2 ml. of the concentrate to 20 ml. of water. This composition contains high levels of dental enamel reactive Sn(II) over substantial periods of time and yields a substantial reduction in enamel solubility, even after aging. Thus, this composition provides an effective means for caries prophylaxis when used in the usual manner two or more times a day.

The distannous ethane-1-hydroxy-1,1-diphosphonate of this Example can be replaced by distannous propane-2,2-diphosphonate, distannous methanedi-hydroxydiphosphonate, distannous dichloromethylenediphosphonate, distannous bromomethylenediphosphonate, or distannous methanephénylhydroxydiphosphonate in quantities sufficient to provide equivalent Sn(II) levels with good results.

EXAMPLE XXII

Another mouthwash embodiment of the invention is formulated as follows:

Component	% By Weight
Ethanol	35.00
Glycerine	10.00
Laurylamine hydrofluoride	0.72
Stannous chloride	0.016
Distannous methane diphosphonate	0.15
Flavouring	0.16
Saccharin	0.12
Water	Balance
pH adjusted to 6.0.	

5 This mouthwash contains effective concentrations of enamel-reactive stannous tin over a period of several months. When used in the conventional manner in undiluted form this composition substantially reduces enamel solubility and caries incidence.

Distannous nonane-5,5-diphosphonate, distannous decane-1,1-diphosphonate, distannous dodecane-2,2-diphosphonate, distannous tetra- 10 decane-3,3-diphosphonate, or distannous butane-1,1-diphosphonate can be used in place of distannous methane diphosphonate with comparable results.

EXAMPLE XXIII

A chewing gum is prepared having the following composition.

Component	% By Weight
Gum base*	21.50
Sugar	59.50
Corn Syrup (Baume 45)	18.20
Flavouring	q.s.
Sodium fluoride	0.25
Distannous pentadecane-8,8-diphosphonate	0.55
pH adjusted to 4.5	

*Estergum	30 parts
Coumarone resin	45 parts
Latex (dry)	15 parts
Paraffin wax (M.P. 180°F.)	10 parts

This composition provides an effective means for caries prophylaxis when chewed in the conventional fashion. Sufficient stannous and fluoride ion is ionized in the course of chewing in saliva to reduce the solubility of dental enamel.

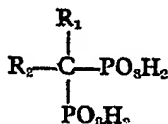
This composition retains high levels of active Sn(II) even after prolonged storage.

The distannous pentadecane-8,8-diphosphonate used in this composition can be replaced by distannous ethane-2-hydroxy-1,1-diphosphonate, distannous decane-1-hydroxy-1,1-diphosphonate, distannous methanebenzylidiphosphonate, distannous ethane-1-methoxy-1,1-diphosphonate or distannous methoxymethylene-diphosphonate with no substantial loss of stability or efficacy.

The distannous gem-diphosphonates employed in each of the foregoing Examples of the application of the salts can also be replaced with distannous ethane-1-acetyl-1,1-diphosphonate or propane-1,3-diphenyl-2,2-diphosphonate with good results.

WHAT WE CLAIM IS:—

1. Distannous salts of gem-diphosphonic acids having the formula



wherein R_1 is hydrogen, halogen, hydroxyl, benzyl, alkyl, hydroxyalkyl, methoxyalkyl or carboxyalkyl and has up to 12 carbon atoms and R_2 is hydrogen, halogen, hydroxyl, acetyl, phenyl, benzyl, alkyl, hydroxyalkyl, methoxyalkyl or carboxyalkyl and has up to 12 carbon atoms.

2. Distannous methane diphosphonate.
3. Distannous ethane-1-hydroxy-1,1-diphosphonate.
4. A distannous salt of a gem-diphosphonic

acid substantially as described in any one of Examples I to III herein.

5. A distannous salt of a gem-diphosphonic acid according to claim 1 and as specifically mentioned herein.

6. An oral composition for caries prophylaxis comprising

(a) at least one water-soluble fluoride in a quantity sufficient to provide from 25 to 4000 parts of fluoride ion per million parts by weight of the composition, and

(b) from 0.05% to 5.0% by weight of at least one distannous salt of a gem-diphosphonic acid of any preceding claim.

7. An oral composition according to claim 6 in which the total stannous tin content is from 15 to 10,000 parts per million parts by weight of the composition.

8. An oral composition according to claim 7 in which the total stannous tin content is from 50 to 8,000 parts per million parts by weight of the composition.

9. A composition according to any one of claims 6 to 8 in which the water soluble fluoride is stannous fluoride.

10. A composition according to claim 9 in which the stannous fluoride is used in an amount sufficient to provide a total amount of at least 300 parts of stannous tin per million parts by weight of the composition.

11. A composition according to any one of claims 6 to 8 in which the water-soluble fluoride is an amine hydrofluoride containing at least one substituted or unsubstituted hydrocarbon radical having from 8 to 20 carbon atoms.

12. An oral composition for caries prophylaxis substantially as described in any one of Examples IV to XXIII herein.

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